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Main Menu | Search Form | Posting Counts | Show S Numbers | Edit S Numbers | Preferences | Cases

Search Results -

Terms	Documents
L16 with l15 with l14 with l6	27

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Search: L17

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Set Name side by side	Query	Hit Count	Set Name result set
DB=USPT,PGPB,JPAB,EPAB,DWPI; PLUR=YES; OP=ADJ			
L17	L16 with l15 with l14 with l6	27	L17
L16	l1 or l4	1417861	L16
L15	AQUEOUS	875317	L15
L14	alcohol or PVA	653344	L14
L13	L12 with l6	3	L13
L12	l4 with l3	53	L12
L11	L10 with l5	16	L11
L10	L8 with l3	3445	L10
L9	L8 and l3	8041	L9
L8	L7 or l1	1452645	L8
L7	peg	68146	L7
L6	dna or plasmid or nucleic or polynucleotide	181920	L6
L5	dna or plasmid or nucleic	175535	L5
L4	microparticle or microsphere	33241	L4
L3	negatively charged lipid or DPSE or DOPE	40676	L3
L2	s negatively charged lipid or DPSE or DOPE	40411	L2
L1	s peg or polymer	1403779	L1

END OF SEARCH HISTORY

his

(FILE 'MEDLINE, CANCERLIT, EMBASE, BIOSIS, BIOTECHDS' ENTERED AT 14:03:35 ON 14 JAN 2003)

DEL HIS

L23	873716	S	POLYME? OR MICROPARTICLE OR MICROSPHERE
L24	536386	S	LIPID OR AMPHIPHILE
L25	9979	S	L24 AND L23
L26	2369734	S	DNA OR NUCLEIC OR PLASMID
L27	2961	S	L26 AND L25
L28	30437	S	PEG
L29	33	S	L28 AND L27
L30	14		DUP REM L29 (19 DUPLICATES REMOVED)
L31	1987	S	PLG
L32	5	S	L31 AND L27
L33	2		DUP REM L32 (3 DUPLICATES REMOVED)
L34	4660255	S	MICRO?
L35	758	S	L34 AND L27
L36	552		DUP REM L35 (206 DUPLICATES REMOVED)
L37	35164	S	ANIONIC OR NEGATIVELY CHARGED LIPID
L38	3822	S	L37 AND L24
L39	413	S	DSPE
L40	10	S	L39 AND L38
L41	5		DUP REM L40 (5 DUPLICATES REMOVED)
L42	53	S	L39 AND L25
L43	27		DUP REM L42 (26 DUPLICATES REMOVED)
L44	40	SS	L27 AND (L37 OR L39)
L45	23		DUP REM L44 (17 DUPLICATES REMOVED)
L46	2932	S	MICROPARTICLE
L47	16	S	L46 AND L27
L48	11		DUP REM L47 (5 DUPLICATES REMOVED)
L49	4686	S	ALCHOHOL OR PVA
L50	67	S	L49 AND L23 AND L26
L51	44		DUP REM L50 (23 DUPLICATES REMOVED)
L52	194289	S	AQUEOUS
L53	334	S	L52 AND L49
L54	169	S	L53 AND L23
L55	7	S	L54 AND L26
L56	5		DUP REM L55 (2 DUPLICATES REMOVED)

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L51 ANSWER 31 OF 44 MEDLINE DUPLICATE 11
AN 97013588 MEDLINE
DN 97013588 PubMed ID: 8860424
TI Polyvinyl derivatives as novel interactive **polymers** for controlled gene delivery to muscle.
AU Mumper R J; Duguid J G; Anwer K; Barron M K; Nitta H; Rolland A P
CS Department of Gene Delivery, GENEMEDICINE, INC., The Woodlands, Texas 7738-4248, USA.
SO PHARMACEUTICAL RESEARCH, (1996 May) 13 (5) 701-9.
Journal code: 8406521. ISSN: 0724-8741.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199703
ED Entered STN: 19970313
Last Updated on STN: 19970313
Entered Medline: 19970304
AB PURPOSE. **DNA** plasmids (pDNA) can be taken up by and expressed in striated muscle after direct intramuscular injection. We have developed interactive **polymeric** gene delivery systems that increase pDNA bioavailability to muscle cells by both protecting pDNA from nucleases and controlling the dispersion and retention of pDNA in muscle tissue. METHODS. A **DNA plasmid**, containing a CMV promoter and a galactosidase reporter gene (CMV-beta-gal), was injected either in saline or formulated in polyvinyl pyrrolidone (PVP) and polyvinyl alcohol (**PVA**) solutions. Interactions between PVP and pDNA were assessed by dynamic dialysis, Isothermal Titration Calorimetry (ITC), and Fourier Transformed Infra Red (FT-IR) spectroscopy. Formulations (50 mu l) were injected into rat tibialis muscles after surgical exposure. Immunohistochemistry for beta-gal was used to visualize the sites of expression in muscle. RESULTS. Beta-gal expression using pDNA in saline reached a plateau while beta-gal expression using PVP formulations increased linearly in the dose range studied (12.5-150 mu g pDNA injected) and resulted in an increase in the number and distribution of cells expressing beta-gal. The interaction between PVP and pDNA was found to be an endothermic process governed largely by hydrogen-bonding and results in protection of pDNA from extracellular nucleases. CONCLUSIONS. Significant enhancement of gene expression using interactive polyvinyl-based delivery systems has been observed. The improved tissue dispersion and cellular uptake of pDNA using polyvinyl-based systems after direct injection into muscle is possibly due to osmotic effects.

L51 ANSWER 25 OF 44 MEDLINE DUPLICATE 10
AN 1998350566 MEDLINE
DN 98350566 PubMed ID: 9685949
TI Protective interactive noncondensing (PINC) **polymers** for enhanced **plasmid** distribution and expression in rat skeletal muscle.
AU Mumper R J; Wang J; Klakamp S L; Nitta H; Anwer K; Tagliaferri F; Rolland A P
CS Gene Delivery Sciences and Biology/Pharmacology, GeneMedicine, Inc., The Woodlands, TX 77381-4248, USA.. mumper@genemedicine.com
SO JOURNAL OF CONTROLLED RELEASE, (1998 Mar 2) 52 (1-2) 191-203. Journal code: 8607908. ISSN: 0168-3659.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199808
ED Entered STN: 19980820
Last Updated on STN: 19980820
Entered Medline: 19980813
AB We have developed protective interactive noncondensing (PINC) **polymers**, such as poly(N-vinyl pyrrolidone) (PVP) and poly(vinyl alcohol) (**PVA**), to protect plasmids from extracellular nuclease degradation while allowing the flexible complex to diffuse throughout the muscle tissue. Molecular modeling, zeta potential modulation, and ethidium bromide intercalation studies were performed to assess the mechanism of interaction between PVP and **plasmid**. The effect of salt concentration, pH, and **polymer-plasmid** ratios were investigated. We have correlated these variables with beta-galactosidase (beta-gal) expression after intramuscular administration to rats. PVP can form hydrogen bonds with the base pairs within the major groove of **DNA** at pH 4.0. The PVP-**plasmid** interaction results in a complex that is more hydrophobic (less negatively charged) than the uncomplexed **plasmid** due to the vinyl backbone of PVP. Up to a ten-fold enhancement in gene expression in rat muscle over the use of 'naked' **DNA** has been demonstrated using these systems. A linear structure-activity relationship (SAR) was found between the percent vinyl pyrrolidone monomer content in poly (vinyl pyrrolidone-covinyl acetate) **polymers** and beta-gal expression in muscle. Modulation of the interaction between PINC **polymers** and **plasmid** directly impacts the levels of gene expression in vivo. The linear SAR is being used to design novel PINC **polymers** with enhanced binding affinity to plasmids.

L51 ANSWER 21 OF 44 MEDLINE DUPLICATE 8
AN 1999356090 MEDLINE
DN 99356090 PubMed ID: 10425333
TI Influence of formulation parameters on the characteristics of poly(D, L-lactide-co-glycolide) microspheres containing poly(L-lysine) complexed **plasmid DNA**.
AU Capan Y; Woo B H; Gebrekidan S; Ahmed S; DeLuca P P
CS Hacettepe University, Faculty of Pharmacy, Department of Pharmaceutical Technology, 06100, Ankara, Turkey.
SO JOURNAL OF CONTROLLED RELEASE, (1999 Aug 5) 60 (2-3) 279-86.
Journal code: 8607908. ISSN: 0168-3659.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals

L51 ANSWER 14 OF 44 MEDLINE DUPLICATE 3
AN 2002022699 MEDLINE
DN 21345115 PubMed ID: 11451511
TI Poly(lactic acid)-poly(ethylene glycol) nanoparticles as new carriers for the delivery of **plasmid DNA**.
AU Perez C; Sanchez A; Putnam D; Ting D; Langer R; Alonso M J
CS Department of Pharmacy and Pharmaceutical Technology, University of Santiago de Compostela, Campus Sur, 15705 Santiago de Compostela, Spain.
SO JOURNAL OF CONTROLLED RELEASE, (2001 Jul 10) 75 (1-2) 211-24.
Journal code: 8607908. ISSN: 0168-3659.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200203
ED Entered STN: 20020121
Last Updated on STN: 20020324
Entered Medline: 20020322
AB The purpose of the present work was to produce and characterize poly(lactic acid)-poly(ethylene glycol) (PLA-PEG) nanoparticles (size lower than 300 nm) containing a high loading of **plasmid DNA** in a free form or co-encapsulated with either poly(vinyl alcohol) (**PVA**) or poly(vinylpyrrolidone) (PVP). The **plasmid** alone or with **PVA** or PVP was encapsulated by two different techniques: an optimized w/o/w emulsion-solvent evaporation technique as well as by a new w/o emulsion-solvent diffusion technique. Particle size, zeta potential, **plasmid DNA** loading and in vitro release were determined for the three **plasmid**-loaded formulations. The influence of the initial **plasmid** loadings (5, 10, 20 microg **plasmid DNA**/mg PLA-PEG) on those parameters was also investigated. The **plasmid** loaded into the nanoparticles and released in vitro was quantified by fluorimetry and the different molecular forms were identified by gel electrophoresis. PLA-PEG nanoparticles containing **plasmid DNA** in a free form or co-encapsulated with **PVA** or PVP were obtained in the range size of 150-300 nm and with a negative zeta potential, both parameters being affected by the preparation technique. Encapsulation efficiencies were high irrespective of the presence of **PVA** or PVP (60-90%) and were slightly affected by the preparation technique and by the initial loading. The final **plasmid DNA** loading in the nanoparticles was up to 10-12 microg **plasmid DNA**/mg **polymer**. **Plasmid DNA** release kinetics varied depending on the **plasmid** incorporation technique: nanoparticles prepared by the w/o diffusion technique released their content rapidly whereas those obtained by the w/o/w showed an initial burst followed by a slow release for at least 28 days. No significant influence of the **plasmid DNA** loading and of the co-encapsulation of PVP or **PVA** on the in vitro release rate was observed. In all cases the conversion of the supercoiled form to the open circular and linear forms was detected. In conclusion, **plasmid DNA** can be very efficiently encapsulated, either in a free form or in combination with PVP and **PVA**, into PLA-PEG nanoparticles. Additionally, depending on the processing conditions, these nanoparticles release **plasmid DNA** either very rapidly or in a controlled manner.

proteins.

L51 ANSWER 9 OF 44 BIOTECHDS COPYRIGHT 2003 THOMSON DERWENT AND ISI
AN 2002-10449 BIOTECHDS
TI **Microparticle** useful for the delivery of bioactive agent, e.g. **nucleic** acid comprises **polymeric** matrix, an anionic and zwitterionic lipid and **nucleic** acid molecule;
useful as a vector to deliver **DNA**, peptide and protein into animal tissue cell for e.g. gene therapy
AU BARMAN S P; MCKEEVER U; HEDLEY M L
PA ZYCOS INC
PI WO 2001093835 13 Dec 2001
AI WO 2000-US17971 2 Jun 2000
PRAI US 2000-208830 2 Jun 2000
DT Patent
LA English
OS WPI: 2002-188239 [24]
AB DERWENT ABSTRACT:
NOVELTY - A **microparticle** having diameter of less than 100 microns, comprising a **polymeric** matrix (a), a lipid (l1) having a pKa of less then 2.5 or a zwitterionic lipid (l2) and a **nucleic** acid molecule (c), is new. The **microparticle** is not encapsulated in a liposome and does not comprise a cell.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following: (1) preparation comprising the novel **microparticle**; (2) administering a **nucleic** acid to an animal by introducing the **microparticle** into the animal; and (3) preparing the **microparticle**, comprising: (a) providing a first solution containing (a) and (l1); (b) providing a second solution containing (c) dissolved or suspended in a solvent; (c) mixing the first and second to form a first emulsion; and (d) mixing the first emulsion with a third solution to form a second emulsion, where (3) and (4) are carried out in a manner that minimizes sharing of the **nucleic** acid while producing microparticles having an average diameter smaller than 100 microns.

USE - For delivering bioactive agent e.g. peptide, protein or **nucleic** acid into cells.

ADMINISTRATION - The **microparticle** is introduced into a mucosal tissue (preferably vaginal or rectal tissue) of the animal. The **microparticle** can be delivered orally, nasally, intralesionally, subcutaneously, intradermally or intramuscularly. No dosage is suggested.

ADVANTAGE - The **microparticle** is act as a highly effective vehicle for the delivery of bioactive agents into cells.

EXAMPLE - To prepare lipid-containing microparticles, poly-lactic-co-glycolic acid (PLGA) (200 mg) was dissolved in methylene chloride (DCM) (7 ml). The resulting PLGA/DCM solution was poured into a 35 ml polypropylene cylindrical tube. OVOTHIN (RTM) (lipid solution) was added to the PLGA/DCM solution to a final concentration of 0.05 % (vol/vol). Polyvinyl alcohol (**PVA**) (1 %; 50 ml) and 0.05 % **PVA**/300 Mm sucrose solution (100 ml) was poured into the above solution and homogenized. pBVKCMluc **DNA** (1.2 mg) in tris-HCl-EDTA (ethylenediaminetetraacetic acid)(TE)/10 % sodium dodecyl sulfate (SDS) (300 ml) was added to the PLGA/DCM solution. The mixture was homogenized for 2 minutes to form a **DNA**/PLGA emulsion. The **DNA**/PLGA emulsion was then immediately poured into 1% **PVA** solution and homogenized for 1 minutes. The mixture was then poured into the beaker containing 0.05 % **PVA** on the stir plate and stirred for two hours. The mixture was then centrifuged. The pelleted microparticles were washed twice with water. After second washing the pellet was resuspended in water, frozen in liquid nitrogen and lyophilized for at least 11 hours. **DNA** from microparticles prepared using TE/sucrose was present in a concentration of 2.33

micro-g/m (**DNA**/PLGA) and 55 % supercoiling, whereas **DNA** from microparticles prepared using OVOTHIN (RTM) was present at a concentration of 1.66 micro-g/ml and 60 % supercoiling.(100 pages)

L56 ANSWER 1 OF 5 BIOTECHDS COPYRIGHT 2003 THOMSON DERWENT AND ISI
AN 2002-11585 BIOTECHDS
TI Novel **nucleic** acid delivery system useful for preparation of composition for delivering **nucleic** acid to subject and for treating/preventing cancer, comprises **DNA** encapsulated in biodegradable **polymeric** microspheres;
recombinant vector-mediated gene transfer and expression in host cell for use in recombinant vaccine and **nucleic** acid vaccine preparation and cancer prevention, therapy and gene therapy
AU JOHNSON M E; MOSSMAN S; CECIL T; EVANS L
PA CORIXA CORP
PI WO 2002003961 17 Jan 2002
AI WO 2000-US21780 7 Jul 2000
PRAI US 2000-216604 7 Jul 2000
DT Patent
LA English
OS WPI: 2002-257248 [30]
AB DERWENT ABSTRACT:
NOVELTY - A **nucleic** acid delivery system (I) comprising deoxyribonucleic acid (**DNA**) encapsulated in biodegradable **polymeric** microspheres, where at least 50% of the **DNA** comprises supercoiled **DNA**, and where at least 50% of the **DNA** is released from the microspheres after 7 days at about 37 degrees C, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following: (1) encapsulating (M) **nucleic** acid molecules in microspheres by dissolving a **polymer** in a solvent to form a **polymer** solution, adding an **aqueous** solution containing **nucleic** acid molecules to the **polymer** solution to form a primary emulsion, homogenizing the primary emulsion, mixing the primary emulsion with a process medium comprising a stabilizer to form a secondary emulsion, and extracting the solvent from the secondary emulsion to form microspheres encapsulating **nucleic** acid molecules; (2) a pharmaceutical composition (II) comprising **nucleic** acid molecules encapsulated in microspheres produced by (M); and (3) use of an aminoalkyl glucosaminide 4-phosphate (AGP) (III) for the preparation of an adjuvant for enhancing the immunostimulatory efficacy of microspheres encapsulating **nucleic** acid molecules.

WIDER DISCLOSURE - Also disclosed is an adjuvant for modulating the immunostimulatory efficacy of microspheres encapsulating **nucleic** acid molecules comprising aminoalkyl glucosaminide 4-phosphate (AGP).

BIOTECHNOLOGY - Preferred System: In (I), the microspheres have an encapsulation efficiency of at least about 40%. At least about 70% of the **DNA** is released from the microspheres after 7 days at about 37 degrees C. At least about 90% of the microspheres are about 1-10 microm in diameter. The microspheres comprise poly(lacto-co-glycolide) (PLG). (I) further comprises an adjuvant comprising AGP. The **DNA** encodes an antigen such as her2/neu associated with cancer, preferably breast cancer or an antigen such as TbH9 associated with infectious disease, preferably tuberculosis. Preferred Method: In (M), the **polymer** comprises PLG including ester end groups or carboxylic acid end groups. The PLG has a molecular weight of from about 8-65 kDa. The **nucleic** acid molecules are maintained at about 2-35 degrees C, preferably 4-25 degrees C prior to the extraction. The solvent comprises dichloromethane, chloroform, or ethylacetate. The **polymer** solution further comprises a cationic lipid, and an adjuvant comprising MPL. The stabilizer comprises carboxymethylcellulose (CMC), polyvinyl alcohol (**PVA**), or a mixture of CMC and **PVA**, and a cationic lipid. The stabilizer comprises from about 1-5% of the process medium. The solvent comprises an internal water volume of from about 0.001-0.5%. The **aqueous** solution comprises

an ethanol content of from about 0-75% (v/v). The **nucleic** acid molecule comprises **DNA**. The **aqueous** solution comprises about 0.2-12 mg/ml **DNA** comprising a **plasmid** of about 3-9 kb. The **aqueous** solution further comprises an adjuvant such as QS21, and a stabilizer comprising bovine serum albumin. At least 50% of the **DNA** retains a supercoiled formation through the extraction step. The encapsulation efficiency is at least about 40%. The microspheres release at least about 50% of the **nucleic** acid molecules within about 7 days, preferably 4 days. Preferred Composition: (II) further comprises an adjuvant such as AGP. Preferred Adjuvant: (III) comprises an **aqueous** formulation. (III) is preferably 517, 527, 547, 557 or 568. (III) is administered simultaneously with the microspheres, or before or after administration of the microspheres.

ACTIVITY - Cytostatic; tuberculostatic.

MECHANISM OF ACTION - Enhancer of immunostimulatory efficacy of microspheres encapsulating **nucleic** acid molecules (claimed); vaccine; gene therapy. Immune responses elicited in monkeys by encapsulated **DNA** was tested: The immune responses elicited in rhesus macaques following three immunizations, at monthly intervals, with either naked TbH9-VR1012 **DNA** or TbH9-VR1012 **DNA** encapsulated in microspheres were tested. Naked **DNA** consisted of 3.3 mg **plasmid** + 40 microg RC527-AF, immunized by intradermal and intramuscular routes. Microspheres **DNA** consisted of 3 mg **plasmid** + 50 microg RC 568-Af delivered intramuscularly. There were four animals in each group. The results, demonstrated that the **microsphere**-encapsulated **DNA** elicited stronger immune responses than were observed with naked **DNA**.

USE - (I) is useful for the preparation of a composition for delivering a **nucleic** acid molecule to a subject, for eliciting an immune response to an antigen in a subject, for treating or preventing a cancer associated with her2/neu antigen or tuberculosis in a subject. (III) is useful for the preparation of an adjuvant for enhancing the immunostimulatory efficacy of microspheres encapsulating **nucleic** acid molecules (claimed). (I) is useful for delivery of vaccines, preferably **DNA** vaccines.

ADMINISTRATION - (II) is administered by parenteral (e.g., intravenous, subcutaneous, intramuscular), buccal, sublingual, rectal, oral, nasal, topical (e.g., transdermal, ophthalmic), vaginal, pulmonary, intraarterial, intraperitoneal, intraocular, or intranasal route or directly into a specific tissue. No dosage details are given.

ADVANTAGE - (I) offers, in one system, a combination of high encapsulation efficiency, rapid release kinetics and preservation of **DNA** in supercoiled form.

EXAMPLE - The formulation of a **DNA** poly(lacto-co-glycolide) (PLG) microspheres with desirable in vitro characteristics was as follows. Specifically, 1-10 microm diameter microspheres which were able to release their **DNA** contents over the course of a week were prepared using a process that resulted in a high encapsulation efficiency (60-80%) and high rate of retention of the **DNA** supercoiled state (70%). PLG microspheres containing **DNA** encoding antigenic proteins were prepared using variations on the double emulsion technique (J.H. Eldridge et al. Mol Immunol, 28:287-294, 1991; S. Cohen et al. Pharm Res, 8:713-720, 1991)). Specifically, **plasmid DNA** in Tris-ethylenediaminetetraacetic acid (EDTA) buffer, 0.38 ml ethanol were combined and brought up to a volume of 5.1 ml using Tris-EDTA buffer. This was the internal (water) phase. 1200 mg of PLG **polymer** was dissolved in 13.9 ml of dichloromethane (DCM) and put on ice. The internal **aqueous** phase was added to the PLG solution and mixed in a 30 ml syringe while still on ice using a Polytron tissue homogenizer for 20 seconds to form the primary emulsion (water-in-oil). The secondary emulsion was prepared

by adding the primary emulsion to a beaker containing 280 ml of 1.4% carboxymethylcellulose), or process medium, on ice, and mixing. The secondary emulsion was diluted with miliQ water, and mixed in order to extract dichloromethane from, and to harden, the microspheres. The resulting microspheres were washed and centrifuged. After washing, mannitol was added to the concentrated microspheres, which were frozen and lyophilized. Lyophilized microspheres were then assayed for their size distribution, **DNA** content, release kinetics, and the supercoiled content of the encapsulated **DNA**. Two plasmids were used in this study, one encoding a tuberculosis antigen, TbH9, and the other encoding the breast cancer antigen, Her-2/neu. Mice were immunized with **DNA** microspheres dispersed in **aqueous** buffer.
The combination of microspheres with selected aminoalkyl glucosaminide 4-phosphate (AGP) was investigated by using a sub-optimal immunization schedule, a single 10 microg dose of encapsulated **DNA** dispersed in phosphate buffer saline (PBS) along with 10 microg of adjuvant. Lastly, the effect of the resuspension buffer was examined by administering to mice a single 10 microg dose of encapsulated **DNA** dispersed in either PBS or sodium chloride free phosphate buffer (PB). The process resulted in microspheres that were small (about 1-10 microm in diameter), with rapid release kinetics, high encapsulation efficiency (40-80%), and good retention of supercoiled **DNA**. More than 33% of the **microsphere** contents were released after 48 hours in vitro at 37 degrees C, more than 50% were released after 4 days, and more than 70% after 7 days. The ratio of supercoiled-to-nicked **DNA** for the **plasmid** extracted from the microspheres was more than 50% of the ratio of the input **DNA**. (60 pages)